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ORIGINAL ARTICLE

Drug-coated balloon angioplasty for de novo small vessel disease including chronic total occlusion and bifurcation in real-world clinical practice

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Abstract
The aim of this study is to validate the efficacy of drug-coated balloons (DCBs) for real-world de novo small vessel diseases including chronic total occlusion and bifurcation. DCB angioplasty has been reported to be effective in the treatment of de novo small vessel disease. However, the number of reports that have focused on complex lesions is limited. This observational study comprised consecutive patients who underwent DCB angioplasty for de novo small vessel disease with a reference diameter of less than 2.5 mm by visual estimation. Outcome parameters included late lumen loss, restenosis rate, and major adverse cardiac events, such as cardiac death, non-fatal myocardial infarction, and target lesion revascularization (TLR). Fifty-two patients underwent DCB angioplasty for 59 lesions with a reference vessel diameter of 1.93 ± 0.63 mm. Thirty-eight of the lesions (69%) were classified as type B2/C, including chronic total occlusions (20%) and bifurcations (33%). At the 8-month follow-up, late lumen loss was − 0.01 ± 0.44 mm with a restenosis rate of 20%. No cardiac deaths or myocardial infarctions were reported and only 5 (9%) angiographically driven TLRs were reported. DCB angioplasty offered an acceptable 8-month lumen patency and a stable clinical outcome for real-world complex de novo coronary diseases.

Keywords Drug-coated balloon · De novo small vessel disease · Chronic total occlusion · Bifurcation

Introduction

Drug-eluting stents have revolutionized percutaneous coronary intervention (PCI) by overcoming restenosis, which has been a significant issue since the development of stent technology. However, drug-eluting stents have introduced new issues, such as stent thrombosis and neoatherosclerosis, which are likely due to chronic inflammation caused by stent strut components followed by delayed and incomplete endothelialization.

A drug-coated balloon (DCB) can be used to deliver antiproliferative drugs to vessel walls without utilizing polymers or alloys and is a theoretically promising device to overcome stent-related problems. Clinical studies, including randomized trials, have demonstrated the efficacy of DCBs for in-stent restenosis [1–3]. We also expect DCBs to perform favorably for native coronary arteries and especially small vessels, which are prone to restenosis due to limited acute gain with stenting. A prior study that evaluated the efficacy of DCBs for small coronary arteries suggested DCBs as alternatives to drug-eluting stent implants [4]. The use of DCBs has been evaluated by several clinical studies [5–9]. However, the number of studies on complex lesions is limited. Therefore, we aimed to validate the efficacy of DCBs for a wide range of de novo small vessel diseases including chronic total occlusions (CTOs) and bifurcation lesions in our daily clinical practice.

Methods

Study design and population

This observational study comprised consecutive patients who underwent PCI using DCBs for de novo small vessel diseases with reference diameters of less than 2.5 mm by visual estimation in our hospital between June 2014 and April 2017. DCBs were applied to the lesions which each

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operator judged as suitable for the DCB angioplasty based on the angiographical findings such as residual stenosis and dissection after predilation [10]. The small vessel lesions which were bailed out by stenting for a major dissection after predilation were not included in the study population. CTOs were defined as complete or nearly complete occlusions (i.e., Thrombolysis in Myocardial Infarction [11] grades 0–1 flow) for at least 3 months [12]. Bifurcation lesions were classified according to the Medina classification [13]. Patients were clinically diagnosed according to the definition of the Japanese Cardiovascular Interventional Therapeutics (CVIT): stable angina, in which patients have stable symptoms for a month without pain at rest; unstable angina which comprises new-onset or increasing angina within a month, resting angina and post-infarction angina which persists within a month after the index myocardial infarction; myocardial infarction with ST-elevation or without, in which patients have continuous chest symptoms and an increase in cardiac biomarkers; silent myocardial ischemia, in which no associated symptoms exist within a month with a detection of segmental myocardial ischemia by stress electrocardiography or imaging modalities; prior myocardial infarction, in which no associated symptoms exist within a month with either an emergence of new abnormal q wave in more than two contiguous leads or a detection of segmental non-viable myocardium by imaging modalities. The indication of revascularization was considered individually as described in the guideline of the Japanese Circulation Society [14] and in the expert consensus document of the CVIT [15]. This study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients.

Intervention procedure

Patients were pretreated with 100 mg aspirin and a P2Y12 inhibitor of either 75 mg clopidogrel or 3.75 mg prasugrel before the elective procedure. In cases of emergent procedure, patients received a loading dose of either 300 mg of clopidogrel or 20 mg of prasugrel in addition to 100 mg of aspirin immediately before the intervention if they had not been placed on dual anti-platelet therapy. Intravenous heparin was administered in boluses of 6000–10,000 IU followed by the addition of the treatment agent to achieve an activated clotting time of 200–250 s. We performed a PCI via a femoral, radial, or brachial approach. After an intracoronary injection of 1.5–2.5 mg isosorbide dinitrate, baseline angiography was performed in views showing the target lesion that was free of foreshortening and overlap. The type of intracoronary imaging used, such as intravascular ultrasound and optical coherence tomography, was selected at the discretion of each operator. Each lesion was dilated with a balloon catheter before the application of a DCB. We then treated the lesion with a paclitaxel-coated balloon (SeQuent Please®, B. Braun Melsungen, Germany). The drug-coated balloon was inflated one time for 60 s with nominal pressure. We finished the procedure when an endpoint of TIMI flow grade 3 and the absence of flow-limiting dissection were observed. A final angiography was performed after the intracoronary administration of isosorbide dinitrate in the same projection as at baseline.

Quantitative coronary angiography

An independent cardiologist quantitatively analyzed angiographic images using a commercially available software (QCA-CMS, Medis, Leiden, The Netherlands) and measured the minimal luminal diameter (MLD), reference vessel diameter (RVD), diameter stenosis (DS), and lesion length (LL) of each lesion. In case of chronic total occlusion, the lesion was evaluated during either antegrade or retrograde filling of the distal vessel. When we failed to calculate lesion length and reference vessel diameter in chronic total occlusion lesion in QCA analysis using preprocedural angiogram, we used the first angiogram in which the vessel lumen was recanalized after the initial predilation with a small-diameter (1.0–1.5 mm) balloon to measure the length and the reference vessel diameter of the chronic total occlusion lesions.

Follow-up

Patients continued dual anti-platelet therapy of 100 mg aspirin and a P2Y12 inhibitor of either 75 mg clopidogrel or 3.75 mg prasugrel for at least 3 months after DCB angioplasty, followed by single anti-platelet therapy of either drug. All patients were clinically followed up for 8 months and underwent angiographic restudy 8 months after the index procedure or depending on clinical symptoms.

The angiographic endpoints were late lumen loss, which was calculated as the post-procedure MLD minus the follow-up MLD, and rate of restenosis, defined as a DS greater than 50% by visual estimation. The clinical endpoints consisted of cardiac death, non-fatal myocardial infarction, and target lesion revascularization (TLR). Cardiac death was defined as any death without clear non-cardiac cause. Myocardial infarction was defined as a typical increase of cardiac biomarkers with associated chest pain and electrocardiographic changes of ST segment. TLR was defined as repeat revascularization by PCI or coronary bypass surgery of the previously treated target lesion.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation. Comparisons between two groups were completed using either Student's *t* test or the Mann–Whitney test for continuous variables according to the normality of distribution, which was tested using the Shapiro–Wilk test. Categorical data were expressed as frequencies and/or percentages, and compared using the Chi-squared test or the Fisher's exact test as appropriate. To assess the characteristics of the CTO and the bifurcation groups in the present study, we compared patient, lesion, procedural characteristics, and outcomes between the CTO group and no CTO–no bifurcation group, and between the bifurcation group and no CTO–no bifurcation group. A value of $p < 0.05$ was considered significant. Statistical analyses were performed using PASW Statistics 18.0 software (SPSS Inc., IBM, Chicago, IL).

Results

Patient, lesion, and angiographic characteristics (Tables 1, 2)

During the study period at our hospital, PCIs for de novo small vessel disease using DCBs were performed in 52 patients for a total of 59 lesions. The mean age was 70 ± 7 years, and 69% of the patients were men. Twenty-two of the fifty-two patients (42%) had diabetes. Eight of the fifty-two patients (15%) had chronic kidney disease, including 5 (10%) hemodialysis patients. Clinical diagnoses included stable angina in 21 cases (40%), unstable angina in 6 (12%), non-ST-elevation myocardial infarction in 1 (2%), ST-elevation myocardial infarction in 3 (6%), silent myocardial ischemia in 19 (37%), and prior myocardial infarction in 2 (4%). The targeted vessel was the left anterior descending artery in 16 cases (29%), the right coronary artery in 18 (33%), and the left circumflex artery in 17 (31%). Thirty-eight of the fifty-nine lesions (69%) were the ACC/AHA lesion type B2/C. Lesions with chronic total occlusion and bifurcation constituted 20% ($n = 12$) and 33% ($n = 18$) of the total lesions, respectively. Eight of the eighteen bifurcation lesions (44%) showed (0,0,1), followed by 5 (28%) with (1,1,1), 4 (22%) with (0,1,1), and 1 (6%) with (0,1,0), according to Medina classification. The preprocedure RVD was 1.93 ± 0.63 mm with a LL of 11.43 ± 6.93 mm. The CTO lesions showed smaller preprocedure RVD (1.47 ± 0.42 mm vs 2.11 ± 0.57 mm, $p < 0.01$) and longer LL (18.54 ± 8.75 mm vs 10.38 ± 5.98 mm, $p < 0.01$) compared with no CTO–no bifurcation lesions. The bifurcation lesions included left circumflex and diagonal branch lesions more often than no CTO–no bifurcation group ($p < 0.01$). There were no significant differences in preprocedure RVD (1.91 ± 0.70 mm vs 2.11 ± 0.57 mm, $p = 0.13$) and LL (8.31 ± 2.34 mm vs 10.38 ± 5.98 mm, $p = 0.42$) between the bifurcation group and no CTO–no bifurcation group.

DCB angioplasty technique (Table 2)

All lesions were dilated with a balloon catheter before the application of DCB. Scoring balloons were most frequently used for predilation (Scoreflex®, OrbusNeich, Hong Kong, China, in 63%, Lacrosse NSE®, Goodman Co., Ltd., Nagoya, Japan, in 4%, Cutting balloon®, Boston Scientific, MA, USA in 2%), followed by the conventional semi-compliant balloons (30%). The diameter and length of the predilation balloon was 2.16 ± 0.38 mm and 16.38 ± 4.52 mm, respectively. The predilation balloons were inflated with 9.22 ± 3.85 atm for 35.27 ± 20.13 s. The diameter and length of the DCB used was 2.34 ± 0.35 mm and 21.45 ± 5.67 mm, respectively. The deployment pressure was 7.18 ± 2.08 atm and the balloon inflation time was 59.27 ± 6.27 s. After the DCB angioplasty, no lesion required bailout stenting with all procedures completed using DCB only.

As for bifurcation strategy, eight lesions (44%) were treated with DCB angioplasty for only side branch, followed by DCBs for both main and side branches ($n = 5$, 28%), DCB for only main branch ($n = 2$, 11%), drug-eluting stent for main branch with DCB for side branch ($n = 2$, 11%), and plain old balloon angioplasty for main branch with DCB for side branch ($n = 1$, 6%). A kissing balloon technique was used in one of the true bifurcation (1,1,1) cases, in which two DCBs were dilated simultaneously at the distal bifurcation lesion of right coronary artery.

In CTO cases, all lesions were treated with antegrade angioplasty without the need of retrograde approach. Intravascular imaging modalities such as IVUS or OCT revealed that 10 of the 12 CTO lesions were successfully crossed with guidewires through the vessel true lumen. In one of the remaining two lesions, the guidewire partially passed through subintimal space. In the other lesion, the guidewire passed through intraplaque area outside the true lumen immediately before the exit of the CTO lesion and reentered the true lumen, making double-barrel lumen at the exit of the CTO lesion after balloon angioplasty.

Quantitative coronary angiography (Table 2)

Post-procedure MLD was 1.42 ± 0.37 mm with DS of 30.34 ± 14.53% and acute luminal gain of 0.67 ± 0.41 mm. In CTO group, post-procedure MLD was 1.29 ± 0.22 mm with DS of 32.00 ± 12.22%. The acute luminal gain of the CTO group was larger than that of the no CTO–no bifurcation group (1.12 ± 0.39 mm vs 0.55 ± 0.29 mm, $p < 0.01$). In bifurcation lesions, final MLD was 1.36 ± 0.39 mm with DS of 34.94 ± 17.19%, which were similar to those in no

Table 1 Patient clinical data

	Total	No CTO–no bifurcation	CTO	*p**	Bifurcation	*p**
N	52	29	11		16	
Age, years	70 ± 7	70 ± 7	72 ± 6	0.26	68 ± 8	0.40
Male	36 (69%)	22 (76%)	5 (45%)	0.14	11 (69%)	0.41
Hypertension	38 (73%)	20 (69%)	7 (64%)	0.62	12 (75%)	0.41
Hyperlipidemia	30 (58%)	15 (52%)	6 (55%)	0.57	11 (69%)	0.21
Smoking	27 (52%)	15 (52%)	7 (64%)	0.24	7 (44%)	0.53
Diabetes mellitus	22 (42%)	11 (38%)	6 (55%)	0.41	7 (44%)	0.64
Family history	11 (21%)	4 (14%)	1 (9%)	0.60	6 (38%)	0.07
Chronic kidney disease	8 (15%)	6 (21%)	1 (9%)	0.39	1 (6%)	0.21
Hemodialysis	5 (10%)	5 (17%)	0 (0%)	0.20	0 (0%)	0.10
Peripheral artery disease	6 (12%)	4 (14%)	1 (9%)	0.28	2 (13%)	0.66
Prior coronary intervention	27 (52%)	16 (55%)	4 (36%)	0.18	11 (69%)	0.41
Prior coronary bypass surgery	2 (4%)	2 (7%)	0 (0%)	0.54	0 (0%)	0.42
Number of diseased vessels						
1	33 (63%)	17 (59%)	7 (64%)	0.41	10 (63%)	0.92
2	10 (19%)	7 (24%)	1 (9%)		3 (19%)	
3	9 (17%)	5 (17%)	3 (27%)		3 (19%)	
Diagnosis						
Stable angina	21 (40%)	14 (47%)	3 (27%)	0.203	5 (31%)	0.708
Unstable angina	6 (12%)	3 (10%)	0 (0%)		3 (19%)	
Non-ST-elevation MI	1 (2%)	0 (0%)	1 (9%)		0 (0%)	
ST-elevation MI	3 (6%)	2 (7%)	0 (0%)		1 (6%)	
Silent myocardial ischemia	19 (37%)	8 (27%)	5 (45%)		7 (44%)	
Prior myocardial infarction	2 (4%)	3 (10%)	2 (18%)		0 (0%)	
Clinical follow-up duration, months	8.0 ± 2.4	8.3 ± 2.8	8.1 ± 1.4	0.35	7.4 ± 2.1	0.26
TLR	5 (9%)	1 (3%)	2 (17%)	0.19	2 (11%)	0.31
Angio-driven TLR	5 (9%)	1 (3%)	2 (17%)	0.19	2 (11%)	0.31
Clinically driven TLR	0 (0%)	0 (0%)	0 (0%)	NA	0 (0%)	NA
Non-fatal MI	0 (0%)	0 (0%)	0 (0%)	NA	0 (0%)	NA
Cardiac death	0 (0%)	0 (0%)	0 (0%)	NA	0 (0%)	NA

Continuous data are presented as mean value with standard deviation; categorical data are presented as number (%)

One patient who underwent DCB angioplasty three times for CTO, bifurcation and non-CTO, non-bifurcation lesions was excluded in the two-group comparison analyses

Three patients underwent DCB angioplasty twice for both CTO and bifurcation lesions

CTO chronic total occlusion, *MI* myocardial infarction, *TLR* target lesion revascularization, *DCB* drug-coated balloon

*vs no CTO–no bifurcation group

CTO–no bifurcation group ($p = 0.32$, p = 0.11, respectively). There was no significant difference in acute lumen gain between the bifurcation group and no CTO–no bifurcation group (0.55 ± 0.39 mm vs 0.55 ± 0.29 mm, $p = 0.67$).

Follow-up (Tables 1, 2)

Follow-up angiography was performed in all patients 7.7 ± 2.8 months after the index DCB intervention. The late lumen loss was − 0.01 ± 0.44 mm. The restenosis rate was 20% (12 of 59 lesions).

All patients were clinically followed up in our hospital for 8.0 ± 2.4 months. No cardiac deaths or non-fatal myocardial infarctions were reported during the follow-up period. Angiographically driven TLRs were performed for five restenosis lesions (9%). Of the five lesions, one lesion underwent TLR because of positive ischemia in stress nuclear test. The other four lesions without an objective evidence of myocardial ischemia underwent TLR due to severe degree of restenosis (three total occlusions and one with 90% stenosis). There were no clinically driven TLRs during the follow-up period.

Table 2 Lesion, procedural, and angiographic data

	Total	No CTO–no bifurcation	CTO	*p**	Bifurcation	*p**
N	59	30	12**		18**	
Diseased vessel						
Left anterior descending artery	16 (29%)	9 (31%)	5 (42%)	0.43	2 (11%)	< 0.01
Left circumflex artery	17 (31%)	8 (28%)	1 (8%)		9 (50%)	
Right coronary artery	18 (33%)	12 (41%)	6 (50%)		3 (17%)	
Diagonal branch	4 (7%)	0 (0%)	0 (0%)		4 (22%)	
Lesion ACC/AHA type						
A	5 (9%)	5 (17%)	0 (0%)	<0.01	0 (0%)	0.24
B1	12 (22%)	8 (28%)	0 (0%)		5 (28%)	
B2	26 (47%)	15 (52%)	1 (8%)		11 (61%)	
C	12 (22%)	1 (3%)	11 (92%)		2 (11%)	
Bifurcation	18 (33%)	0 (0%)	1** (8%)		18** (100%)	
Medina classification						
001	8 (15%)				8 (44%)	
111	5 (9%)				5 (28%)	
011	4 (7%)				4 (22%)	
010	1 (2%)				1 (6%)	
Bifurcation strategy						
SB DCB only					8 (44%)	
MB DCB only					2 (11%)	
MB DCB and SB DCB					5 (28%)	
MB DES and SB DCB					2 (11%)	
MB POBA and SB DCB					1 (6%)	
CTO	12 (20%)	0 (0%)	12** (100%)		1** (6%)	
Calcification	8 (24%)	6 (55%)	1 (14%)	0.25	1 (6%)	0.07
Rotational atherectomy	8 (15%)	7 (24%)	1 (8%)	0.26	1 (6%)	0.11
Intravascular ultrasound	35 (64%)	18 (62%)	11 (92%)	0.07	10 (56%)	0.59
Optical coherence tomography	17 (28%)	9 (31%)	2 (17%)	0.32	6 (34%)	0.81
Predilation						
Scoreflex®	35 (63%)	23 (55%)	6 (25%)	0.15	8 (29%)	0.09
Lacrosse NSE®	2 (4%)	0 (0%)	0 (0%)		2 (7%)	
Cutting balloon®	1 (2%)	1 (2%)	0 (0%)		0 (0%)	
Conventional non-compliant balloon	1 (2%)	1 (2%)	1 (4%)		1 (4%)	
Conventional semi-compliant balloon	17 (30%)	17 (40%)	17 (71%)		17 (61%)	
Size, mm	2.16 ± 0.38	2.24 ± 0.42	1.96 ± 0.14	0.05	2.11 ± 0.37	0.34
Length, mm	16.38 ± 4.52	15.86 ± 4.02	18.75 ± 6.78	0.30	16.17 ± 3.90	0.86
Inflation pressure, atm	9.22 ± 3.85	9.70 ± 4.22	11.20 ± 4.24	0.33	8.94 ± 3.54	0.85
Inflation time, s	35.27 ± 20.13	34.14 ± 21.88	33.33 ± 16.14	0.77	41.94 ± 20.16	0.24
Drug-coated balloon (SeQuent Please®)						
Size, mm	2.34 ± 0.35	2.40 ± 0.41	2.38 ± 0.23	0.77	2.22 ± 0.26	0.21
Length, mm	21.45 ± 5.67	21.72 ± 5.55	23.75 ± 5.69	0.31	19.72 ± 5.28	0.17
Inflation pressure, atm	7.18 ± 2.08	7.07 ± 1.98	7.08 ± 2.39	0.92	7.50 ± 2.28	0.87
Inflation time, s	59.27 ± 6.27	58.28 ± 8.37	60.00 ± 0.00	0.75	60.56 ± 2.36	0.10
QCA findings						
Preprocedure						
Reference vessel diameter, mm	1.93 ± 0.63	2.11 ± 0.57	1.47 ± 0.42	<0.01	1.91 ± 0.70	0.13
Minimal lumen diameter, mm	0.76 ± 0.45	0.95 ± 0.40	0.17 ± 0.31	<0.01	0.81 ± 0.22	0.20
Diameter stenosis, %	61.63 ± 20.88	53.62 ± 16.12	90.08 ± 18.11	<0.01	55.65 ± 10.60	0.64
Lesion length, mm	11.43 ± 6.93	10.38 ± 5.98	18.54 ± 8.75	<0.01	8.31 ± 2.34	0.42

Table 2 (continued)

	Total	No CTO–no bifurcation	CTO	*p**	Bifurcation	*p**
N	59	30	12**		18**	
Post-procedure						
Reference vessel diameter, mm	2.09 ± 0.53	2.12 ± 0.54	1.92 ± 0.26	0.23	2.15 ± 0.62	0.96
Minimal lumen diameter, mm	1.42 ± 0.37	1.50 ± 0.40	1.29 ± 0.22	0.13	1.36 ± 0.39	0.32
Diameter stenosis, %	30.34 ± 14.53	27.63 ± 13.67	32.00 ± 12.22	0.34	34.94 ± 17.19	0.11
Acute gain, mm	0.67 ± 0.41	0.55 ± 0.29	1.12 ± 0.39	<0.01	0.55 ± 0.39	0.67
Residual dissection	12 (20%)	5 (17%)	2 (17%)	0.69	5 (28%)	0.29
Follow-up duration, months	7.7 ± 2.8	7.8 ± 2.6	8.2 ± 4.0	0.97	7.2 ± 2.2	0.82
Reference vessel diameter, mm	2.22 ± 0.55	2.17 ± 0.48	2.18 ± 0.53	0.95	2.28 ± 0.73	0.55
Minimal lumen diameter, mm	1.44 ± 0.50	1.55 ± 0.34	1.41 ± 0.63	0.47	1.23 ± 0.59	0.03
Diameter stenosis, %	33.69 ± 20.52	27.22 ± 11.39	34.98 ± 23.98	0.33	43.34 ± 25.90	0.02
Late loss, mm	−0.01 ± 0.44	−0.05 ± 0.31	−0.13 ± 0.61	0.60	0.12 ± 0.47	0.34
Binary restenosis	12 (20%)	2 (7%)	2 (17%)	0.32	8 (44%)	<0.01

Continuous data are presented as mean value with standard deviation; categorical data are presented as number (%)

CTO chronic total occlusion, *ACC* American College of Cardiology, *AHA* American Heart Association, *SB* side branch, *MB* main branch, *DCB* drug-coated balloon, *DES* drug-eluting stent, *POBA* plain old balloon angioplasty, *QCA* quantitative coronary angiography

*vs no CTO–no bifurcation group

**One patient with a CTO at bifurcation was duplicated

CTO lesions (Fig. 1)

Eleven patients with the twelve chronic total occlusions demonstrated an average late lumen loss of −0.13 ± 0.61 mm. Binary restenosis rate of the CTO lesions was not statistically different from that of no CTO–no bifurcation lesions (17% vs 7%, $p = 0.32$). Two lesions (17%) exhibited restenosis and underwent repeat coronary interventions, because they exhibited a total occlusion and a severe restenosis of 90%. The TLR rate of the CTO group was not different from that of no CTO–no bifurcation (17% vs 3%, $p = 0.19$). There were no cardiac deaths or non-fatal myocardial infarctions during the follow-up periods. Of the two CTO lesions where the guidewire had not passed through the entire true lumen, one lesion which had been treated with partial subintimal angioplasty using DCB kept the vessel lumen patency at 7-month follow-up angiogram. The other CTO lesion which had been left with double-barrel lumen at the exit of the CTO after the index DCB angioplasty developed severe restenosis that was revascularized with a drug-eluting stent.

Bifurcation lesions (Fig. 2)

In 18 bifurcation lesions of 16 patients, the late lumen loss was 0.12 ± 0.47 mm, which was not significantly different from that of no CTO–no bifurcation lesions ($p = 0.34$). However, due to significantly smaller MLD (1.23 ± 0.59 mm vs 1.55 ± 0.34 mm, $p = 0.03$) and larger DS (43.34 ± 25.90% vs 27.22 ± 11.39%, $p = 0.02$), binary restenosis rate of the bifurcation lesions was significantly higher than that of no CTO–no bifurcation lesions (44% vs 7%, $p < 0.01$). Of the 8 restenoses (44%), two lesions (11%) underwent revascularization with coronary intervention, because they exhibited total occlusions. The TLR rate of the bifurcation group was not statistically different from that of no CTO–no bifurcation group (11% vs 3%, $p = 0.31$). There were no cardiac deaths or non-fatal myocardial infarctions in patients with bifurcation lesions.

Discussion

We demonstrated (1) that DCB angioplasty in daily clinical practice offered acceptable late lumen loss and even positive lumen enlargement at an 8-month follow-up for de novo small vessel diseases including complex lesion subsets such as chronic total occlusions and bifurcations and (2) that patients treated with DCB did not experience cardiac death or non-fatal myocardial infarction and only experienced low rates of restenosis and TLR during an 8-month follow-up period.

The present study corroborates the results of the previous studies that reported positive effects of DCB for small vessel diseases [4–9]. Furthermore, the favorable results were achieved among real-world patients with complex lesions. The type B2 and C lesion accounted for 69% of the total population in the present study, which was larger than that of any other previous studies reporting DCB efficacy [4, 7–9].

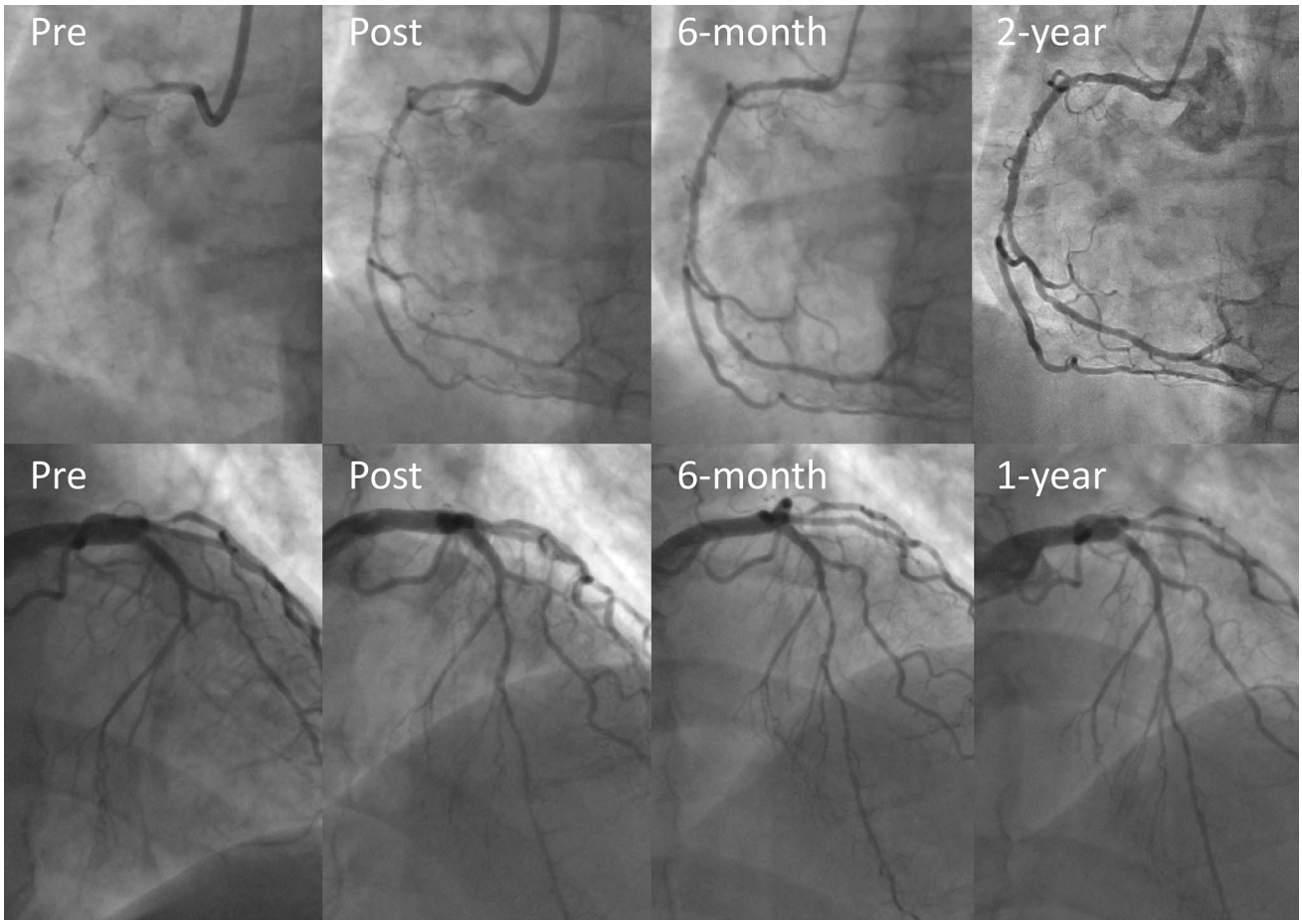

Fig. 1 Two representative cases of DCB angioplasty for chronic total occlusions. Upper row: mid-right coronary artery lesion was predilated with 2.5-mm scoring balloon followed by 2.5–20-mm SeQuent Please®. Follow-up angiography showed patency at 2 years. Lower row: mid-left anterior descending artery lesion was predilated with 2.0-mm scoring balloon followed by 2.5–20-mm SeQuent Please®. Follow-up angiography revealed patency at 1 year. *DCB* drug-coated balloon

We observed low late lumen loss and even positive lumen enlargement after drug-eluting balloon angioplasty. Theoretically, an inhibition of neointimal proliferation by paclitaxel is considered to play a pivotal role in this phenomenon. In addition, based on a previous IVUS study indicating that 73% of late lumen loss after balloon angioplasty were due to vessel negative remodeling, whereas 27% were due to intimal proliferation [16], DCBs might affect the vessel remodeling process in addition to inhibiting intimal proliferation. Future imaging studies should use optical coherence tomography and intravascular ultrasound to clarify the mechanism of this phenomenon after DCB angioplasty. Another possible explanation for the observed lumen preservation and even enlargement after DCB angioplasty is the restoration of vasomotor function. Due to the absence of residual prostheses within vessel walls, vasodilatory functions may have been preserved after DCB-only angioplasty. Late lumen enlargement, especially observed in chronic total occlusion subsets, could have partly represented flow-mediated vasodilation after restoring coronary flow with angioplasty.

A previous study showed that DCB plus bailout bare-metal stenting had larger late lumen loss than DCB-only angioplasty [7]. In addition, because the number of studies reporting DCB plus bailout drug-eluting stent is limited [17, 18], a lack of understanding of vessel response to double dose of anti-proliferative drugs derived from both a DCB and a drug-eluting stent raises safety concerns over the DCB plus bailout drug-eluting stent. Therefore, we have tried to complete the DCB procedure without stenting. Predilation with a scoring balloon followed by 1-min DCB inflation with nominal pressure offered the favorable outcome. In addition to the balloon angioplasty technique, a judgement of a need for bailout stent is important in case of vessel dissection after DCB application. We need further investigation to establish practical criteria for this issue.

Even in the contemporary drug-eluting stent era, chronic total occlusions remain challenging issues. The treatment of

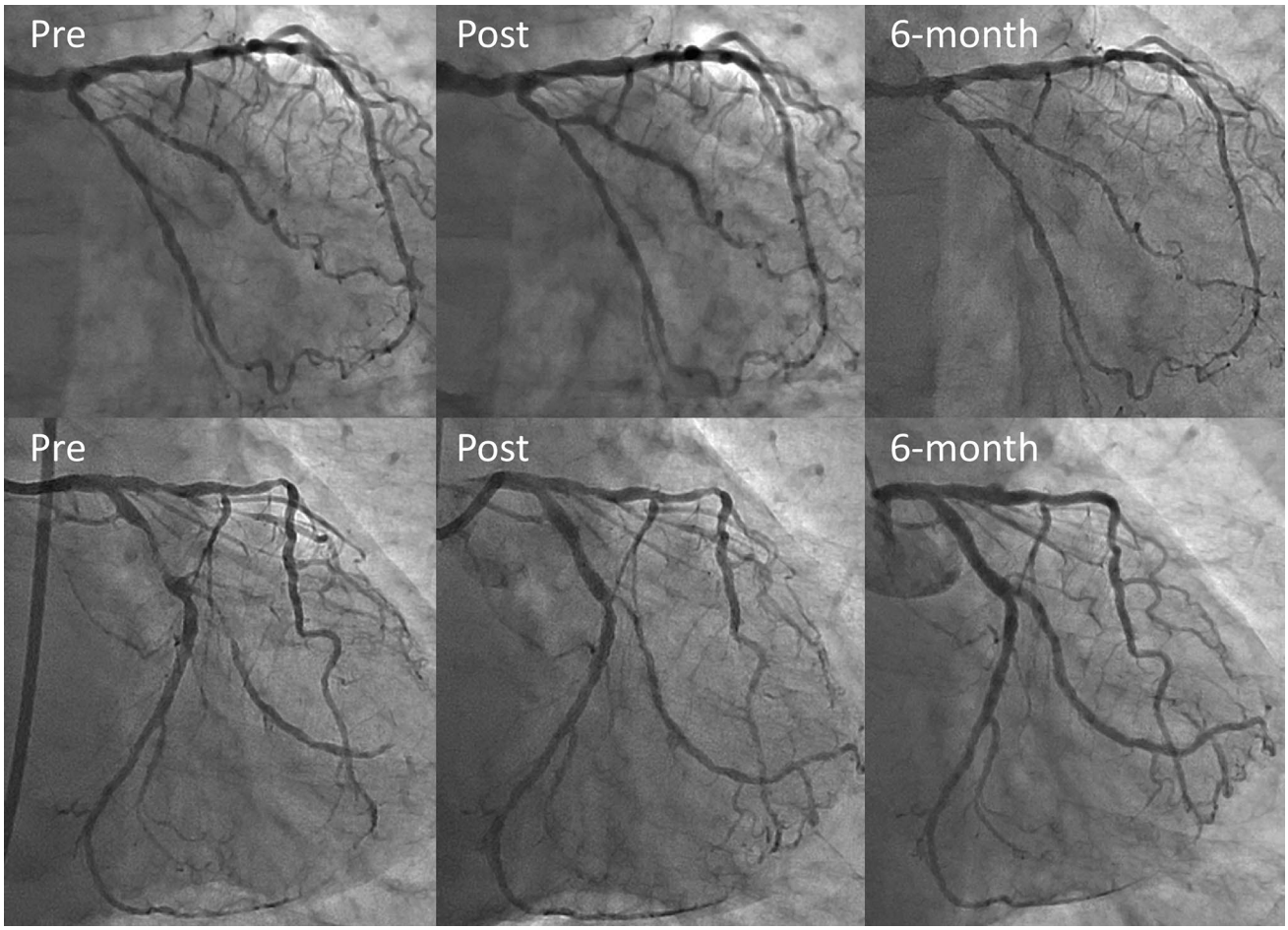

Fig. 2 Two representative cases of DCB angioplasty for bifurcation lesions. Upper row: proximal lesion of obtuse marginal branch was predilated with 2.0-mm scoring balloon followed by 2.0–15-mm SeQuent Please®. Follow-up angiography showed lumen patency and even enlargement at 6 months. Lower row: proximal lesion of obtuse marginal branch was predilated with 2.0-mm semi-compliant balloon followed by 2.0–30-mm SeQuent Please®. Follow-up angiography demonstrated not only patency but also lumen enlargement at 6 months. Proximal left circumflex artery lesion was treated with a drug-eluting stent. *DCB* drug-coated balloon

the lesions may at times require multiple stents, which may lead to stent-related problems, such as restenosis, thrombosis, and fracture, in the long term. The acceptable restenosis rate of 17% and the positive luminal enlargement (i.e. late lumen loss of -0.13 ± 0.61 mm) in the present study are in line with a previous study which evaluated a drug-coated balloon only approach for chronic total occlusion and showed a restenosis rate of 11.8% with a late lumen gain of 0.11 ± 0.49 mm [19]. These results indicate the feasibility of DCB angioplasty for chronic total occlusion. In the present study, small vessel CTO lesions with the lesion length around 18 mm which gained adequate lumen diameter after DCB angioplasty showed the acceptable restenosis rate. Furthermore, 83% of the CTO lesions (10 out of 12) were successfully crossed with guidewires through the vessel true lumen. This finding indicates that a small vessel CTO lesion with the length up to 18 mm where a guidewire crosses through the true vessel lumen and an angioplasty obtains adequate lumen diameter can be treated by DCB effectively. Furthermore, we decided the use of DCB after we confirmed favorable angiographic results after predilation. Therefore, the lesions analyzed in the present study do not reflect all real-world CTO lesions but are limited ones which were well prepared before DCB application. As to whether the present findings can be generalized to a wide range of CTO lesions, we need further investigation.

In the bifurcation lesion analysis, despite the acceptable late lumen loss of 0.12 ± 0.47 mm, the restenosis rate was 44%. This was due to the small acute lumen gain (0.55 ± 0.39 mm) after the DCB angioplasty. Most of the bifurcation DCB angioplasties (89%) involved ostial lesion of the side branch in the present study, therefore, it was difficult to obtain acute lumen gain without vessel scaffolding devices. In addition, because of the real-world registry nature without stipulating strict procedural protocols, DCBs were applied to inadequately predilated lesions which did not

fulfill criteria such as residual stenosis less than 30% before DCB application, recommended by the German Drug-Eluting Balloon Consensus Group [10], leading to final diameter stenosis as high as 35%. To obtain lumen diameter large enough to prevent restenosis after DCB angioplasty without causing flow-limiting major dissection, debulking devices might offer favorable effects. We need further investigation and innovation for the bifurcation lesion. In comparison with restenosis rate of 0–24.2% reported in the previous studies on DCB use for bifurcation lesions [20–23], that of 44% in the present study was higher. However, it is difficult to simply compare those results, because lesion locations and intervention strategies were not same among them. The former two studies evaluated a strategy of DCB for both main and side branches followed by bare-metal stent deployment in main branch [20, 21], and the latter two studies employed a DCB angioplasty for side branch with main branch drug-eluting stent implantation [22, 23]. In the present study, cases with drug-eluting stent in main branch and DCB in side branch accounted for only 11%. Further studies evaluating how best various types of bifurcation lesions can be treated with DCB angioplasty are needed.

The low incidence of major adverse cardiac events after DCB angioplasty is possibly related to the stable endothelialization of the dilated lesions due to the absence of residual prostheses within vessel walls. Although drug-eluting stents are highly effective devices, the treatment requires the use of residual prostheses within vessel walls, which could lead to adverse clinical events. The proposed DCB intervention promotes vessel healing without the use of such residual prostheses. In addition to the development of stent technology, we should further develop balloon angioplasty techniques using DCBs.

Limitations

This study was a single-center observational study with a small sample size. However, all consecutive patients with various lesions that were unsuitable for stent deployment due to the small vessel size and were treated with DCB angioplasty were analyzed without any exclusion. Furthermore, all patients underwent angiographic restudies at the chronic phase. The present study is useful for assessing the efficacy and safety of DCB interventions in real-world clinical practice. In addition, due to the nature of observational study, the present study fails to show the number of total small vessel lesions in which DCB angioplasty was planned at first before predilation. During the study period, 343 lesions were treated with stents less than 2.5 mm in diameter in our hospital. Assuming that DCB applications were initially considered for all those lesions before predilation, the rate of DCB application for de novo small vessel disease was 15% (59 of 402) at a minimum. Of the 250 type B2/C lesions, 41 lesions (16%) were treated with DCBs, while the other 209 type B2/C lesions (84%) were treated with stents. Therefore, it is difficult to generalize the results of the present study to all small vessel lesions. The present study indicates that we can expect acceptable outcomes for small vessel lesions which are treated by DCB-only angioplasty with no need for bailout stenting after predilation. We need to further evaluate randomized comparison trials and a larger scale patient registry to elucidate whether the favorable results reported herein can be generalized to a wide range of small vessel coronary lesions. Further studies using intracoronary imaging devices, such as optical coherence tomography and intravascular ultrasound, are required to further probe vessel response after DCB angioplasty and to improve DCB angioplasty techniques to achieve better clinical outcomes. In the present study, no lesion required additional stenting after the DCB angioplasty. As the number of DCB angioplasty cases increases, the chance of needing bailout stenting will increase. We need to clarify actual rate of bailout stenting after DCB angioplasty in real-world clinical practice and to investigate treatment strategy to deal with suboptimal results after DCB angioplasty.

Conclusions

Drug-coated balloon angioplasty in daily clinical practice demonstrated acceptable late lumen loss and even positive lumen enlargement at the 8-month follow-up for de novo small vessel diseases including chronic total occlusions and bifurcation lesions. The restenosis rate was also acceptable for the small vessel diseases except bifurcation lesion which needs further research. Clinically, low rates of TLR without cardiac death or non-fatal myocardial infarction were reported during the 8-month follow-up.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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